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10/590,606	08/24/2006	Shifeng Pan	P1151US10	8958

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EXAMINER	
COUGHLIN, MATTHEW P	
ART UNIT	**PAPER NUMBER**
4131	

NOTIFICATION DATE	DELIVERY MODE
06/24/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/590,606	PAN ET AL.	
	Examiner	Art Unit	
	Matthew P. Coughlin	4131	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-12 are pending in the application.

Election/Restrictions

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The following compounds are representative of the species claimed:

The compound of claim 1 where Y is a phenyl ring, the compound of claim 1 where Y is a pyridyl ring, and the compound of claim 1 where Y is a thiophene ring.

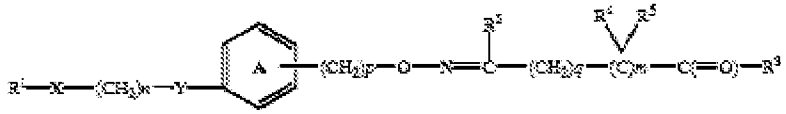
Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

The following claim(s) are generic: Claims 1 and 12.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:
The species lack unity of invention because even though the species require the technical feature of a bicyclic oxime, this technical feature is not a

special technical feature as it does not make a contribution over the prior art in view of U.S. Patent No. 6,251,926 by Momose et al. Momose et al. teach the following genus:



where R^4 may form a ring with R^2, see column 104, claim 1.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

During a telephone conversation with Scott Reid on May 27th, 2009 a provisional election was made of the compound of example 1 (depicted below) **with traverse.** Affirmation of this election must be made by applicant in replying to this Office action.

Applicant's elected Example 1

Applicant has made an election of species in the instant case. Pursuant to the provisions of MPEP 803.02 and the unity of invention test set out by the CCPA in 1980 (*In re Harnisch*, 631 F.2d 716, 206 USPQ 300) the scope of the search has been limited to the following substituents of the base structure of Formula I:

Y is a phenyl ring, substituted as defined in claim 1,

X is C_{2-4} alkylene or alkenylene,

R_1 is a phenyl ring,

and all other substituents are as defined within the instant claims.

The remaining subject matter of claim 1 that is not drawn to the above elected invention stands withdrawn under 37 CFR 1.142(b) as being for non-elected subject matter. The remaining compounds which are not within the elected invention, which are independent and distinct from the elected invention and do not have unity with the elected compound and are therefore withdrawn by means of a restriction requirement within the claims are, for example, the compounds of the formula I wherein W is any of the diverse heterocyclic ring systems claimed, etc.

The above mentioned withdrawn compounds which are withdrawn from consideration as being for nonelected subject matter differ materially in structure and composition from the compounds of the elected invention. The withdrawn compounds differ from those of the elected invention, such as by the presence of the heterocyclic rings as R_1, etc. which are chemically recognized to differ in structure and function. This recognized chemical diversity of the compounds can be seen by the various classifications of these compounds in the U.S. classification system. Therefore, again, the compounds which are withdrawn from consideration as being for non-elected subject matter differ materially in structure and composition and have been restricted properly as a reference which anticipated but the elected subject matter would not even render obvious the non-elected subject matter.

These withdrawn compounds are independent and distinct from the elected invention and do not have unity with the compound elected and are therefore withdrawn by means of a restriction requirement within the claims.

Priority

This application is a 35 U.S.C. 371 National Stage Filing of International Application No. PCT/US05/06123, filed February 24th 2005, which claims priority under 35 U.S.C. 119(e) to Provisional Application No. 60/547712, filed February 24th, 2004.

Specification

Applicant is reminded of the proper content of an Abstract of the Disclosure.

In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." Exemplification of a species could be illustrative of members of the class. For processes, the type reaction, reagents and process conditions should be stated, generally illustrated by a single example unless variations are necessary.

The abstract of the disclosure is objected to because it neither provides for the general nature of the compound(s) nor exemplifies any members or formulae illustrative of its class. Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 11 is rejected under 35 U.S.C. 101 because claim 11 provides for the use of a compound of claim 1, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely

recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 9 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 provides for the use of a compound of claim 1, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 1 recites that "R_5 is hydrogen, C_{1-6}alkyl and $-C(O)R_6$." It is suggested that Applicant amend the claim to read "R_5 is selected from hydrogen, C_{1-6}alkyl and $-C(O)R_6$" or "R_5 is hydrogen, C_{1-6}alkyl or $-C(O)R_6$" to conform to standard Markush language.

Claim 1 recites the limitation of "isomers;" however, this term has not been defined in the specification beyond stating that stereoisomers and geometric isomers are within the scope of the invention. The standard interpretation of the generic term isomers is any of two or more substances that are composed of the same elements in the same proportions but differ in properties because of differences in the arrangement of atoms. From this definition, any compound with the same element count as compounds according to Formula I would be within the scope of the claims. It is suggested that

Applicant amend the claim to remove this limitation or specifically claim types of isomers that have support in the specification, such as geometric and optical isomers.

Claim 1 is further rejected because it recites the limitation of a "prodrug" where Applicant has defined a prodrug in the specification to according to Saulnier et al., (1994), Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985. Saulnier et al. define prodrugs as bioreversible derivatives and provide one example of a prodrug. From this definition, the metes and bounds of the term “prodrug” are indefinite. Prodrugs in general and as noted in Saulnier et al., are compounds, which undergo *in vivo* conversion to parent active drugs. In that sense, recitation of prodrug is acceptable; however, the definitions of various variable groups (such as A) include structural and functional groups, namely esters, and therefore the difference between these variable groups and the prodrug groups is not clear. There is clear-cut ambiguity as to what is to be considered as prodrug and what is not. Applicants should note that if the variable groups are prodrug moieties, which are in general inactive but becomes active upon *in vivo* transformation, then the compound bearing the variable group would be deemed as inactive which is not what the claim recites.

Furthermore, the issue of second paragraph is whether the structures of the claimed compounds are clearly defined. Applicants’ prodrugs are molecules whose structure may lie outside the subject matter of the compounds of formula (I), but upon metabolism in the body are converted to active compounds falling within the structural scope of compounds of formula (I). The claim describes the function intended but provides no specific structural guidance to what constitutes a "prodrug". Structural formulas, names, or both can accurately describe organic compounds, which are the subject matter of

claim 1. Attempting to define means by function is not proper when the means can be clearly expressed in terms that are more precise.

Claims 9 and recite the limitation of an "animal;" however Applicant has not defined this term in the specification. It is unclear where Applicant considers a human subject an animal. It is suggested that Applicant clearly define the subject being treating by the instant methods.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds of claim 1 and pharmaceutically acceptable salts thereof, does not reasonably provide enablement for a solvate or hydrate of a compound of formula I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in making an enablement rejection are summarized as:

a) the quantity of experimentation necessary,

b) the amount of direction or guidance presented,

c) the presence or absence of working examples,

d) the nature of the invention,

e) the state of the prior art,

f) the relative skill of those in the art,

g) the predictability or unpredictability of the art, and

h) the breadth of the claims.

In re Colianni, 195 USPQ 150 (CCPA 1977). *In re Rainer*, et al., 146 USPQ 218 (CCPA 1965). *Ex parte Formal*, 230 USPQ 546 (BPAI 1986).

a) Determining if a particular compound would form a solvate would require synthesis and recrystallization of the compound solvate using a variety of solvents, temperatures and humidities. The experimentation for solvates is potentially open-ended.

b) The specification merely mentions the Applicant's intention to make solvates, without teaching the preparation thereof.

c) While the claims recite solvates, no working examples show their formation. As stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190, 1194 (Fed.Cir. 1993):

> The specification purports to teach, with over fifty examples, the preparation of the claimed compounds ... However ... there is no evidence that such compounds exist ... [T]he examples ... do not produce the postulated compounds ... [T]here is ... no evidence that such compounds even exist.

The specification shows no evidence of the formation and actual existence of solvates. Hence, Applicant must show formation of solvates or limit the claims accordingly.

d) The nature of the invention is chemical synthesis of solvates, which involves chemical reactions.

e) The state of the art recognizes that the formation, composition and therapeutic activity of solvates is unpredictable. The Federal Circuit has recognized a solvate as an example of a polymorph or pseudopolymorph (emphasis added):

> "Polymorphs" are distinct crystalline structures containing the same molecules. These structural differences can affect various

> properties of the crystals, such as melting points and hardness (e.g., graphite and diamonds are both crystalline forms of carbon) .... [P]seudopolymorphs are often loosely called polymorphs ... Pseudopolymorphs not only have their molecules arranged differently but also have a slightly different molecular composition. A common type of pseudopolymorph is a solvate, which is a crystal in which the molecules defining the crystal structure "trap" molecules of a solvent. The crystal molecules and the solvent molecules then bond to form an altered crystalline structure.

SmithKline Beecham Corp. v. Apotex Corp., 74 USPQ2d 1398, 1409 (Fed.Cir. 2005). The same rationale applies for hydrates; solvates in which the solvent is water. Souillac, et al., Characterization of Delivery Systems, Differential Scanning Calorimetry, pages 217-218 (in Encyclopedia of Controlled Drug Delivery, 1999, John Wiley & Sons, pages 212-227), recognize that different polymorphs of the same drug can have different therapeutic activity (emphasis added):

> Because different polymorphic forms of the same drug exhibit significant differences in their physical characteristics, therapeutic activity from one form to another may be different. Studying the polymorphism of a drug and the relative stability of the different polymorphs is a critical part of pre-formulation development.

Further, Vippagunta et al. (Advanced Drug Delivery Reviews, 48 (2001), pages 3-26) state “Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated in to the crystal lattice of a compound is complex and difficult.” See page 18, section 3.4.

f) The artisan using Applicant’s disclosure to prepare the claimed solvates would be, e.g., an experienced process chemist with at least a BS chemistry degree.

g) Chemical reactions are known as unpredictable. *In re Marzocchi, et al.*, 169 USPQ 367, 370 (CCPA 1971); *In re Fisher*, 166 USPQ 18, 24 (CCPA

1970). See above regarding the unpredictability of solvate and hydrate formation.

h) The breadth of the claims includes thousands of compounds of the instant formula I as well as presently unknown compounds embraced by the terms solvates. See MPEP 2164.01(a), discussed supra, justifying the conclusion of lack of enablement commensurate with the claims. Undue experimentation will be required to practice Applicant's claimed invention.

Claims 1-12 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for compounds of formula I, pharmaceutically acceptable salts thereof and pharmaceutical compositions thereof, where X = $-(CH_2)_2-$, or $-(CH_2)_3)-$, W = $-CH_2-$, R_1 = phenyl substituted by C_6 cycloalykyl and optionally substituted by CH_3 or CF_3, A = $-CO_2H$, Z = azetidine, $-NHCH_2CH_2$, or 1-ethyl piperazine does not reasonably provide enablement for compounds of formula I, pharmaceutically acceptable salts thereof and pharmaceutical compositions thereof, where X ≠ $-(CH_2)_2-$, or $-(CH_2)_3)-$, W ≠ $-CH_2-$, R_1 ≠ phenyl substituted by C_6 cycloalykyl and optionally substituted by CH_3 or CF_3, A ≠ $-CO_2H$, Z ≠ azetidine, $-NHCH_2CH_2$, or 1-ethyl piperazine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention(s) commensurate in scope with these claims. The compounds of formula I, pharmaceutically acceptable salts thereof and pharmaceutical compositions thereof, where X ≠ $-(CH_2)_2-$, or $-(CH_2)_3)-$, W ≠ $-CH_2-$, R_1 ≠ phenyl substituted by C_6 cycloalykyl and optionally substituted by CH_3 or CF_3, A ≠ $-CO_2H$, Z ≠ azetidine, $-NHCH_2CH_2$, or 1-ethyl piperazine, as recited in claim 1, have not been adequately enabled in the specification to allow any person having ordinary skill in the art, at the time this invention was made, to

make and use the compounds of formula I, pharmaceutically acceptable salts thereof and pharmaceutical compositions thereof, where X ≠ $-(CH_2)_2-$, or $-(CH_2)_3)-$, W ≠ $-CH_2-$, R_1 ≠ phenyl substituted by C_6 cycloalykyl and optionally substituted by CH_3 or CF_3, A ≠ $-CO_2H$, Z ≠ azetidine, $-NHCH_2CH_2$, or 1-ethyl piperazine.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is *undue*. These factors include, but are not limited to: (a) breadth of the claims; (b) nature of the invention; (c) state of the prior art; (d) level of one of ordinary skill in the art; (e) level of predictability in the art; (f) amount of direction provided by the inventor; (g) existence of working examples; and (h) quantity of experimentation needed to make or use the invention based on the content of the disclosure. (See *Ex parte Forman* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

The above factors, regarding the present invention, are summarized as follows:

(a) *Breadth of the claims* - the breadth of the claims includes all of the tens of thousands of compounds of claim 1, pharmaceutically acceptable salts thereof and pharmaceutical compositions thereof of the formula I, shown in claim 1;

(b) *Nature of the invention* - the nature of the invention is drawn to compounds of formula I, methods of using them for treating or preventing diseases mediated by the EDG/S1P receptor and methods of synthesizing said compounds;

(c) *State of the prior art - Nature Reviews: Drug Discovery* offers a snapshot of the state of the drug development art. Herein, drug development is stated to follow the widely accepted Ehrlich model which includes: 1) development of a broad synthetic organic chemistry program; 2) subsequent testing of compounds in an appropriate laboratory model for the disease to be treated; and 3) screening of compounds with low toxicity in prospective clinical

trials (Jordan, V. C. *Nature Reviews: Drug Discovery*, 2, **2003**, p. 205);

(d) *Level of one of ordinary skill in the art* - the artisans synthesizing applicant's compounds of formula I, pharmaceutically acceptable salts thereof and pharmaceutical compositions thereof, where X ≠ $-(CH_2)_2-$, or $-(CH_2)_3)-$, W ≠ $-CH_2-$, R_1 ≠ phenyl substituted by C_6 cycloalykyl and optionally substituted by CH_3 or CF_3, A ≠ $-CO_2H$, Z ≠ azetidine, $-NHCH_2CH_2$, or 1-ethyl piperazine, would be a collaborative team of synthetic chemists and/or health practitioners, possessing commensurate degree level and/or skill in the art, as well as several years of professional experience;

(e) *Level of predictability in the art* - Synthetic organic chemistry is quite unpredictable (*In re Marzocchi and Horton* 169 USPQ at 367 ¶ 3). The following excerpt is taken from Dörwald, F. Zaragoza. *Side Reactions in Organic Synthesis: A Guide to Successful Synthesis Design*, Weinheim: WILEY-VCH Verlag GmbH & Co. KGaA, **2005**, Preface:

> *Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why.*
>
> *Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work.*
>
> *Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious).*

(f) *Amount of direction provided by the inventor* - the application is negligent regarding direction with respect to making and using compounds of formula I, pharmaceutically acceptable salts thereof and pharmaceutical compositions thereof, where X ≠ $-(CH_2)_2-$, or $-(CH_2)_3)-$, W ≠ $-CH_2-$, R_1 ≠ phenyl substituted by C_6 cycloalykyl and optionally substituted by CH_3 or CF_3, A ≠ $-CO_2H$, Z ≠ azetidine, $-NHCH_2CH_2$, or 1-ethyl piperazine;

(g) *Existence of working examples* - applicant has provided sufficient guidance to make and use compounds of formula I, pharmaceutically

acceptable salts thereof and pharmaceutical compositions thereof, where X = $-(CH_2)_2-$, or $-(CH_2)_3)-$, W = $-CH_2-$, R_1 = phenyl substituted by C_6 cycloalykyl and optionally substituted by CH_3 or CF_3, A = $-CO_2H$, Z = azetidine, $-NHCH_2CH_2$, or 1-ethyl piperazine; however, the disclosure is insufficient to allow extrapolation of the limited examples to enable the scope of the tens of thousands of compounds of formula I, pharmaceutically acceptable salts thereof and pharmaceutical compositions thereof, where X ≠ $-(CH_2)_2-$, or $-(CH_2)_3)-$, W ≠ $-CH_2-$, R_1 ≠ phenyl substituted by C_6 cycloalykyl and optionally substituted by CH_3 or CF_3, A ≠ $-CO_2H$, Z ≠ azetidine, $-NHCH_2CH_2$, or 1-ethyl piperazine. The specification lacks working examples of compounds of formula I, pharmaceutically acceptable salts thereof and pharmaceutical compositions thereof, where X ≠ $-(CH_2)_2-$, or $-(CH_2)_3)-$, W ≠ $-CH_2-$, R_1 ≠ phenyl substituted by C_6 cycloalykyl and optionally substituted by CH_3 or CF_3, A ≠ $-CO_2H$, Z ≠ azetidine, $-NHCH_2CH_2$, or 1-ethyl piperazine.

Within the specification, "specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. *Markush* claims must be provided with support in the disclosure for each member of the *Markush* group. Where the constitution and formula of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula." See MPEP § 608.01(p).

(h) *Quantity of experimentation needed to make or use the invention based on the content of the disclosure* - predicting whether a recited compound is in fact one that produces a desired physiological effect at a therapeutic concentration and with useful kinetics, is filled with experimental uncertainty, and without proper guidance, would involve a substantial amount of experimentation (Jordan, V. C. *Nature Reviews: Drug Discovery*, 2, **2003**, pp. 205-213).

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. {*In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)}.

The determination that *undue experimentation* would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. (*In re Wands*, 858 F.2d at 737, 8 USPQ2d at

1404). These factual considerations are discussed comprehensively in MPEP § 2164.08 (scope or breadth of the claims), § 2164.05(a) (nature of the invention and state of the prior art), § 2164.05(b) (level of one of ordinary skill), § 2164.03 (level of predictability in the art and amount of direction provided by the inventor), § 2164.02 (the existence of working examples) and § 2164.06 (quantity of experimentation needed to make or use the invention based on the content of the disclosure).

Based on a preponderance of the evidence presented herein, the conclusion that applicant is insufficiently enabled for making and using compounds of formula I, pharmaceutically acceptable salts thereof and pharmaceutical compositions thereof, where X ≠ $-(CH_2)_2-$, or $-(CH_2)_3)-$, W ≠ $-CH_2-$, R_1 ≠ phenyl substituted by C_6 cycloalykyl and optionally substituted by CH_3 or CF_3, A ≠ $-CO_2H$, Z ≠ azetidine, $-NHCH_2CH_2$, or 1-ethyl piperazine, is clearly justified.

Claims 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of breast cancer, transplant rejection, and deregulated angiogenesis, does not reasonably provide enablement for treating or preventing any disease involving the EDG/S1P receptor, any disease mediated by lymphocytes, any T-cell mediated inflammatory or autoimmune disease or any disease mediated by a neo-angiogenesis process. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a

determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue".

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case,

The nature of the invention

The nature of the invention is a drawn to a method of treating or preventing any disease involving the EDG/S1P receptor, any disease mediated by lymphocytes, any T-cell mediated inflammatory or autoimmune disease or any disease mediated by a neo-angiogenesis process using a compound according to formula I.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that the pharmacological art involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence

of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is the more specific enablement is necessary in order to satisfy the statute.

A full analysis of the plethora of diseases instantly claimed cannot be made; however, the following examples demonstrate that Applicant lacks enablement for all diseases claimed.

With respect to Applicant's claim of treating a disease in an animal in which alteration of the EDG/S1P receptor plays a role, the biological role of the EDG/S1P is complex and its varied roles in disease pathways have not been elucidated. Takuwa et al. (Molecular and Cellular Endocrinology 2001, 177, 3-11) have discussed the activities of the EDG family receptors and stated "It is now becoming evident that EDG family S1P receptors play central roles in the pleiotropic activities of S1P in diverse cell types. The elucidation of physiological and pathological roles for the S1P signaling system deserves future investigation." Therefore, a clear understanding of the role of the EDG receptor family in the diverse array of disease Applicant is claiming has not been established. In order to practice said invention, a person having ordinary skill in the art would need to determine which disease respond to

the EDG family of receptors and furthermore, which compounds result in a therapeutic benefit.

With respect to Applicant's claim of treating any inflammatory disease, inflammatory diseases are especially unpredictable due to their complex nature. Note that inflammation is a process that can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammatory responses arise. Mediators include (but are not limited to) bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

With respect to Applicant's claim of preventing a disease mediated by lymphocytes, attention is drawn to the fact that HIV infection results in the decrease of lymphocytes. Therefore, Applicant presently claims a method for the prevention of HIV. While the concept of preventing HIV has been addressed, there is presently no known therapeutic method for preventing HIV infection. Indicated in a review by Graham, B.S., ("Clinical trials of HIV vaccines." *HIV Molecular Immunology Database* **2000**. Edited by: Korber BT, Brander C, Haynes BF, Koup R, Kuiken C, Moore JP, Walker BD, and Watkins D. Published by: Theoretical Biology and Biophysics Group, Los Alamos National Laboratory, Los Alamos, NM. pp. I-20-38), "the ultimate vaccine that can prevent persistent HIV-1 infection will probably require a conceptual breakthrough…" (p. I-26).

The amount of direction present and the presence or absence of working examples

Applicant has provided pharmacological data and procedure for an *in vitro* assay of antitumor activity against a mouse breast cancer cell line, an *in vitro* EDG1-S1P1 binding assay, an *in vitro* FLIPR calcium flux assay, an *in vivo* (mouse) assay for the measurement of blood lymphocyte depletion, and an *in vivo* (mouse) assay for anti-angiogenic activity on pages 27-30 of the instant specification

The breadth of the claims

The breadth of the claims covers a vast number of diseases that are identified by underlying biochemical pathway involved in the disease state. Furthermore, the diseases covered include yet undiscovered disorders that could have varied molecular pathways.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine which of the many diseases claimed are alleviated by administration of the claimed compounds.

The level of the skill in the art

The level of skill in the art is high; however, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* or *in vivo* screening to determine whether the compounds

instantly claimed exhibit the desired pharmacological activity for the diverse range of diseases claimed.

The specification fails to provide sufficient support of the broad use of the claimed compounds of the invention in a method of treating or preventing a disease involving the EDG/S1P receptor, any disease mediated by lymphocytes, any T-cell mediated inflammatory or autoimmune disease or any disease mediated by a neo-angiogenesis process. As a result necessitating one of skill to perform an exhaustive search for which diseases can be treated by what compounds of the invention in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compounds encompassed in the instant claims, with no assurance of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

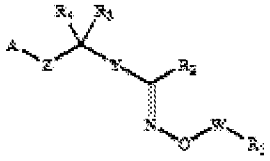
Claims 1-12 are rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent Application Publication No. US 2009/0036423 A1 ('423) by Pan et al. in view of U.S. Patent No. 5,674,879 by Manning et al. in further view of Mu et al. J. Med. Chem. 2002, 45, 4774-4785.

The applied reference ('423) has four common inventors with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior

art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Determining the scope and contents of the prior art. (See MPEP § 2141.01)

Pan et al. teach compounds and preparations thereof of the following genus:



Prior art genus

where the variables A, W, Y, Z, R_1, R_3 and R_4 encompass the definitions instantly claimed for Applicant's genus (depicted below) for use in treating immune diseases.

Instantly claimed genus

Ascertainment of the differences between the prior art and the claims. (See MPEP § 2141.02)

The two differences between the prior art and the claims are that:

(1) Applicant claims a variable "n" that allows for repeated carbon linkers, for instance $-CH_2-$ when R_2 and R_3 are hydrogen, and

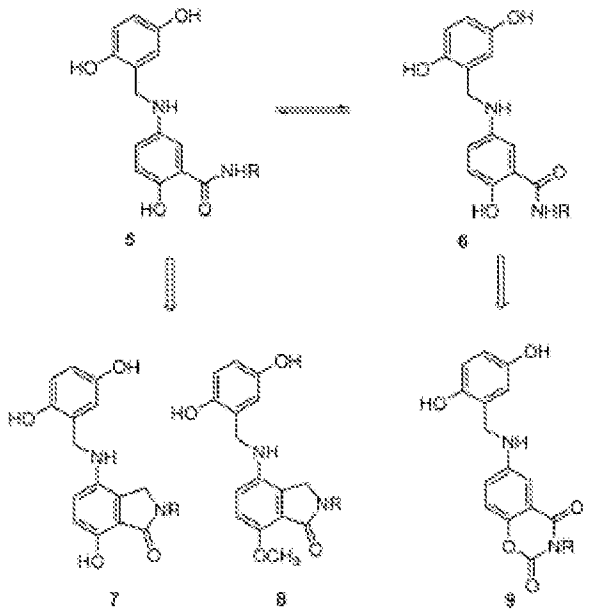
(2) Applicant's core contains a bicycle where the prior art teaches that R_2 is not incorporated into a fused ring system with "Y."

Finding of prima facie obviousness --- rationale and motivation (See MPEP § 2141.02)

With respect to the difference that Applicant claims a variable "n" that allows for repeated carbon linkers, MPEP 2144.09 states "Compounds which are ... homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by $-CH_2-$ groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such

compounds possess similar properties. In re Wilder, 563 F.2d 457, 195 USPQ 426 (CCPA 1977). Therefore, a person having ordinary skill in the art at the time the invention was made would have been motivated to synthesize homologs of the prior art with the reasonable expectation that these compounds would have similar immunosuppressant activity. NOTE: While Applicant claims a repeating group, the subject matter overlaps when the instantly claimed variable "n" is one.

With respect to the difference that Applicant's core contains a bicycle where the prior art teaches that R_2 is not incorporated into a fused ring system with “Y,” the act of conformationally restricting functional groups in biological molecules is well known in the medicinal chemistry art. Manning et al. teach the general concept by stating that “Compounds which conformationally restrict the possible orientations of the pharmacophores incorporated therein may maximize the interaction between those pharmacophores and the bind site of the receptor subtype or subtypes of interest.” See column 2, lines 34-38. Furthermore, Mu et al. teach that conformational restriction can be accomplished upon incorporation into a bicyclic ring. See Chart 1, page 4775 (reproduced below).

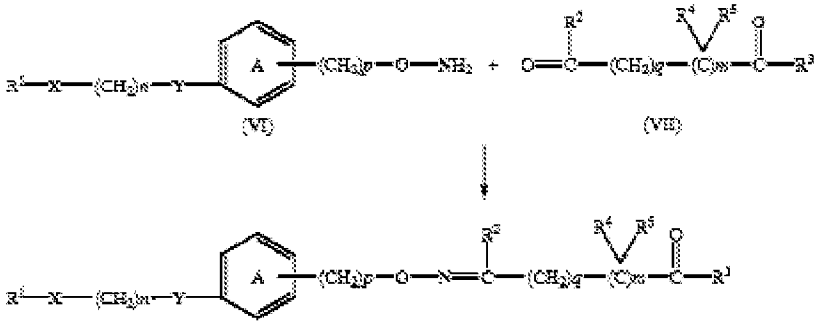


In the report from Mu et al., the conformation of a carbonyl group was restricted upon incorporation into a bicyclic compound. Since Pan et al. teach the oxime core in the genus and in each example compounds, a person having ordinary skill in the art at the time the invention was made would have recognized that this core structure likely contributes to biological activity. Since the use of conformational restriction is aimed at locking the functional group of interest into a conformation that interacts favorably with the biological target, a person having ordinary skill in the art at the time the invention was made would have been motivated to incorporate the oxime structure into a bicyclic structure with the adjacent aryl ring with the aim of discovering compounds which show improved biological activity, for instance, as immunosuppressants.

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,251,926 by Momose et al.

Determining the scope and contents of the prior art. (See MPEP § 2141.01)

Momose et al. teach the synthesis of structurally related compounds in column 30 (reproduced below).



In the above reaction R_2 may incorporated into a ring with R_4. See claim 1.

Ascertainment of the differences between the prior art and the claims. (See MPEP § 2141.02)

The difference between the procedure taught by Momose et al. and the instantly claimed process is that the compounds used by Momose et al. are not identical to those instantly claimed but are analogous. Note each process involved the preparation of bicyclic oxime compounds where one of the cycle is an aryl group and the other is a saturated carbocycle.

Finding of prima facie obviousness --- rationale and motivation (See MPEP § 2141.02)

The use of analogous reactants in a known process is *prima facie* obvious. *In re Durden*, 226 USPQ 359 (1985). Once the general reaction has been shown to be old, the burden is on Applicants to present reasons or authority for believing that a group on the starting material would take part in or affect the basic reaction and thus alter the nature of the product or the operability of the process. In looking at the instant claimed process as a whole, as stated in *In re Ochiai*, 37 USPQ 2d 1127 (1995), the claimed process would have been suggested to one skilled in the art.

One skilled in the art would thus be motivated to utilize the process of the prior to arrive at the instant claimed process with the expectation of producing oxime immunosuppressant agents. The instant claimed invention would have been suggested to one skilled in the art and therefore, the instant claimed invention would have been obvious to one skilled in the art.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 and 13-15 of copending Application No. 12/024992 in view of U.S. Patent No. 5,674,879 by Manning et al. in further view of Mu et al. J. Med. Chem. 2002, 45, 4774-4785. See rationale for first 103 rejection made above.

This is a provisional obviousness-type double patenting rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Matthew P. Coughlin whose telephone number is (571)270-1311. The examiner can normally be reached on Monday through Thursday from 7:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JAMES O. WILSON can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Matthew P. Coughlin/
Examiner, Art Unit 4131

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624